	~~Chi t 5; component VI~~	~~16~~	~~C~~	~~P02224~~
	~~Chi t 6.01; component VIIA~~	~~16~~	~~C~~	~~P02226~~
	~~Chi t 6.02; component IX~~	~~16~~	~~C~~	~~P02223~~
	~~Chi t 7; component VIIB~~	~~16~~	~~C~~	~~P02225~~
	~~Chi t 8; component VIII~~	~~16~~	~~C~~	~~P02227~~
	~~Chi t 9; component X~~	~~16~~	~~C~~	~~P02228~~
~~Dolichovespula maculata (white face hornet)~~	~~Dol m 1; phospholipase A1~~	~~35~~	~~C~~	~~100. Soldatova, L., L. Kochoumian, and T.P. King. 1993. Sequence similarity of a hornet (D. maculata) venom allergen phospholipase A1 with mammalian lipases. FEBS Letters 320:145-149.~~
	~~Dol m 2; hyaluronidase~~	~~44~~	~~C~~	~~101. Lu, G., L. Kochoumian and T.P. King. Whiteface hornet venom allergen hyaluronidase: cloning and its sequence similarity with other proteins (abst.). 1994. J. Allergy Clin. Immunol. 93:224.~~
	~~Dol m 5; antigen 5~~	~~23~~	~~C~~	~~102. Fang, K. S. F., M. Vitale, P. Fehlner, and T. P. King. 1988. cDNA cloning and primary structure of a white-faced hornet venom allergen, antigen 5. Proc. Natl. Acad. Sci., USA 85:895-899.~~ ~~103. King, T. P., D. C. Moran, D. F. Wang, L. Kochoumian, and B.T. Chait. 1990. Structural studies of a hornet venom allergen antigen 5, Dol m V and its sequence similarity with other proteins. Prot. Seq. Data Anal. 3:263-266.~~
~~Dolichovespula arenaria (yellow hornet)~~	~~Dol a 5; antigen 5~~	~~23~~	~~C~~	~~104. Lu, G., M. Villalba, M.R. Coscia, D.R. Hoffman, and T.P. King. 1993. Sequence analysis and antigen cross reactivity of a venom allergen antigen 5 from hornets, wasps and yellowjackets. J. Immunol. 150: 2823-2830.~~
~~Polistes annularies (wasp)~~	~~Pol a 1; phospholipase A1~~	~~35~~	~~P~~	~~105. King, T. P. and Lu, G. 1997. Unpublished data.~~
	~~Pol a 2; hyaluronidase~~	~~44~~	~~P~~	~~105. King, T. P. and Lu, G. 1997. Unpublished data.~~
	~~Pol a 5; antigen 5~~	~~23~~	~~C~~	~~104. Lu, G., M. Villalba, M.R. Coscia, D.R. Hoffman, and T.P. King. 1993. Sequence analysis and antigen cross reactivity of a venom allergen antigen 5 from hornets, wasps and yellowjackets. J. Immunol. 150: 2823-2830.~~
~~Polistes dominulus (Mediterranean paper wasp)~~	~~Pol d 1;~~	~~32-34~~	~~C~~	~~DR Hoffman~~
	~~Pol d 4; serine protease~~			~~DR Hoffman~~
	~~Pol d 5;~~			~~P81656~~
~~Polistes exclamans (wasp)~~	~~Pol e 1; phospholipase A1~~	~~34~~	~~P~~	~~107. Hoffman, D.R. 1992. Unpublished data.~~
	~~Pol e 5; antigen 5~~	~~23~~	~~C~~	~~104. Lu, G., M. Villalba, M.R. Coscia, D.R.~~

				Hoffman, and T.P. King. 1993. Sequence analysis and antigen cross reactivity of a venom allergen antigen 5 from hornets, wasps and yellowjackets. J. Immunol. 150: 2823-2830.
Polistes fuscatus (wasp)	Pol f 5; antigen 5	23	C	106. Hoffman, D.R. 1993. Allergens in hymenoptera venom XXV: The amino acid sequences of antigen 5 molecules and the structural basis of antigenic cross-reactivity. J. Allergy Clin. Immunol. 92:707-716.
Polistes metricus (wasp)	Pol m 5; antigen 5	23	P	106. Hoffman, D.R. 1993. Allergens in hymenoptera venom XXV: The amino acid sequences of antigen 5 molecules and the structural basis of antigenic cross-reactivity. J. Allergy Clin. Immunol. 92:707-716.
Vespa crabo (European hornet)	Vesp c 1; phospholipase	34	P	107. Hoffman, D.R. 1992. Unpublished data.
	Vesp c 5.0101; antigen 5	23	C	106. Hoffman, D.R. 1993. Allergens in hymenoptera venom XXV: The amino acid sequences of antigen 5 molecules and the structural basis of antigenic cross-reactivity. J. Allergy Clin. Immunol. 92:707-716.
	Vesp c 5.0102; antigen 5	23	C	106. Hoffman, D.R. 1993. Allergens in hymenoptera venom XXV: The amino acid sequences of antigen 5 molecules and the structural basis of antigenic cross-reactivity. J. Allergy Clin. Immunol. 92:707-716.
Vespa mandarina (giant asian hornet)	Vesp m 1.01;			DR Hoffman
	Vesp m 1.02;			DR Hoffman
	Vesp m 5;			P81657
Vespula flavopilosa (yellowjacket)	Ves f 5; antigen 5	23	C	106. Hoffman, D.R. 1993. Allergens in hymenoptera venom XXV: The amino acid sequences of antigen 5 molecules and the structural basis of antigenic cross-reactivity. J. Allergy Clin. Immunol. 92:707-716.
Vespula germanica (yellowjacket)	Ves g 5; antigen 5	23	C	106. Hoffman, D.R. 1993. Allergens in hymenoptera venom XXV: The amino acid sequences of antigen 5 molecules and the structural basis of antigenic cross-reactivity. J. Allergy Clin. Immunol. 92:707-716.
Vespula maculifrons (yellowjacket)	Ves m 1; phospholipase A1	33.5	C	108. Hoffman, D. R. 1993. The complete amino acid sequence of a yellowjacket venom phospholipase (abst). J. Allergy Clin. Immunol. 91:187.
	Ves m 2; hyaluronidase	44	P	109. Jacobson, R.S., D.R. Hoffman, and D.M. Kemeny. 1992. The cross-reactivity between bee and vespid hyaluronidases has a structural basis (abst). J. Allergy Clin. Immunol. 89:292
	Ves m 5; antigen 5	23	23	104. Lu, G., M. Villalba, M.R. Coscia, D.R. Hoffman, and T.P. King. 1993. Sequence analysis and antigen cross reactivity of a venom allergen antigen 5 from hornets,

				wasps and yellowjackets. J. Immunol. 150: 2823-2830.
Vespula pennsylvanica (yellowjacket)	Ves p 5; antigen 5	23	C	106. Hoffman, D.R. 1993. Allergens in hymenoptera venom XXV: The amino acid sequences of antigen 5 molecules and the structural basis of antigenic cross-reactivity. J. Allergy Clin. Immunol. 92:707-716.
Vespula squamosa (yellowjacket)	Ves s 5; antigen 5	23	C	106. Hoffman, D.R. 1993. Allergens in hymenoptera venom XXV: The amino acid sequences of antigen 5 molecules and the structural basis of antigenic cross-reactivity. J. Allergy Clin. Immunol. 92:707-716.
Vespula vidua (wasp)	Ves vi 5;	23	C	106. Hoffman, D.R. 1993. Allergens in hymenoptera venom XXV: The amino acid sequences of antigen 5 molecules and the structural basis of antigenic cross-reactivity. J. Allergy Clin. Immunol. 92:707-716.
Vespula vulgaris (yellowjacket)	Ves v 1; phopholipase A1	35	C	105A. King TP, Lu G, Gonzalez M, Qian N and Soldatova L. 1996. Yellow jacket venom allergens, hyaluronidase and phospholipase: sequence similarity and antigenic cross-reactivity with their hornet and wasp homologs and possible implications for clinical allergy. J. Allergy Clin. Immunol. 98:588-600.
	Ves v 2; hyaluronidase	44	P	105A. King TP, Lu G, Gonzalez M, Qian N and Soldatova L. 1996. Yellow jacket venom allergens, hyaluronidase and phospholipase: sequence similarity and antigenic cross-reactivity with their hornet and wasp homologs and possible implications for clinical allergy. J. Allergy Clin. Immunol. 98:588-600.
	Ves v 5; antigen 5	23	C	104. Lu, G., M. Villalba, M.R. Coscia, D.R. Hoffman, and T.P. King. 1993. Sequence analysis and antigen cross reactivity of a venom allergen antigen 5 from hornets, wasps and yellowjackets. J. Immunol. 150: 2823-2830.
Myrmecia pilosula (Australian jumper ant)	Myr p 1,		C	X70256
	Myr p 2;		C	S81785
Solenopsis geminata (tropical fire ant)	Sol g 2;			DR Hoffman
	Sol g 4			DR Hoffman
Solenopsis invicta (fire ant)	Sol i 2;	13	C	110. Hoffman, D.R. 1993. Allergens in Hymenoptera venom XXIV: The amino acid sequences of imported fire ant venom allergens Sol i II, Sol i III, and Sol i IV. J. Allergy Clin. Immunol. 91:71-78. 111. Schmidt, M., R.B. Walker, D.R. Hoffman, and T.J. McConnell. 1993. Nucleotide sequence of cDNA encoding the

				fire ant venom protein Sol i II. FEBS Letters 319:138-140.
	Sol i 3;	24	C	110. Hoffman, D.R. 1993. Allergens in Hymenoptera venom XXIV: The amino acid sequences of imported fire ant venom allergens Sol i II, Sol i III, and Sol i IV. J. Allergy Clin. Immunol. 91:71-78.
	Soli 4;	13	C	110. Hoffman, D.R. 1993. Allergens in Hymenoptera venom XXIV: The amino acid sequences of imported fire ant venom allergens Sol i II, Sol i III, and Sol i IV. J. Allergy Clin. Immunol. 91:71-78.
Solenopsis saevissima (brazilian fire ant)	Sols 2;			DR Hoffman
FOODS				
Gadus callarias (cod)	Gad c 1; allergen M	12	C	112. Elsayed S, Bennich H. The primary structure of Allergen M from cod. Scand J Immunol 3:683-686, 1974. 113. Elsayed S, Aas K, Sletten K, Johansson SGO. Tryptic cleavage of a homogeneous cod fish allergen and isolation of two active polypeptide fragments. Immunochemistry 9:647-661, 1972.
Salmo salar (Atlantic salmon)	Sals 1; parvalbumin	12	C	X97824, X97825
Bos domesticus (domestic cattle)	Bos d 4; alpha-lactalbumin	14.2	C	M18780
	Bos d 5; beta-lactoglobulin	18.3	C	X14712
	Bos d 6; serum albumin	67	C	M73993
	Bos d 7; immunoglobulin	160		77. Gjesing B, Lowenstein H. Immunochemistry of food antigens. Ann Allergy 53:602, 1984.
	Bos d 8; caseins	20-30		77. Gjesing B, Lowenstein H. Immunochemistry of food antigens. Ann Allergy 53:602, 1984.
Gallus domesticus (chicken)	Gal d 1; ovomucoid	28	C	114. Hoffman, D. R. 1983. Immunochemical identification of the allergens in egg white. J. Allergy Clin. Immunol. 71:481-486. 115. Langeland, T. 1983. A clinical and immunological study of allergy to hen's egg white. IV. specific IgE antibodies to individual allergens in hen's egg white related to clinical and immunolgical parameters in egg-allergic patients. Allergy 38:493-500.
	Gald 2; ovalbumin	44	C	114. Hoffman, D. R. 1983.

				~~Immunochemical identification of the allergens in egg white. J. Allergy Clin. Immunol. 71:481-486.~~ ~~115. Langeland, T. 1983. A clinical and immunological study of allergy to hen's egg white. IV. specific IgE antibodies to individual allergens in hen's egg white related to clinical and immunolgical parameters in egg-allergic patients. Allergy 38:493-500.~~
	~~Gald 3; conalbumin (Ag22)~~	~~78~~	~~C~~	~~114. Hoffman, D. R. 1983. Immunochemical identification of the allergens in egg white. J. Allergy Clin. Immunol. 71:481-486.~~ ~~115. Langeland, T. 1983. A clinical and immunological study of allergy to hen's egg white. IV. specific IgE antibodies to individual allergens in hen's egg white related to clinical and immunolgical parameters in egg-allergic patients. Allergy 38:493-500.~~
	~~Gald 4; lysozyme~~	~~14~~	~~C~~	~~114. Hoffman, D. R. 1983. Immunochemical identification of the allergens in egg white. J. Allergy Clin. Immunol. 71:481-486.~~ ~~115. Langeland, T. 1983. A clinical and immunological study of allergy to hen's egg white. IV. specific IgE antibodies to individual allergens in hen's egg white related to clinical and immunolgical parameters in egg-allergic patients. Allergy 38:493-500.~~
	~~Gal d 5; serum albumin~~	~~69~~	~~C~~	~~X60688~~
~~Metapenaeus ensis~~ ~~(shrimp)~~	~~Met e 1; tropomyosin~~		~~C~~	~~U08008~~
~~Penaeus azteeus (shrimp)~~	~~Pen a 1; tropomyosin~~	~~36~~	~~P~~	~~116. Daul, C.B., M. Slattery, J.E. Morgan, and S.B. Lehrer. 1993. Common crustacea allergens: identification of B-cell epitopes with the shrimp specific monoclonal antibodies. In: "Molecular Biology and Immunology of Allergens" (D. Kraft and A. Sehon, eds.). CRC Press, Boca Raton. pp. 291-293.~~
~~Penaeus indicus (shrimp)~~	~~Pen i 1; tropomyosin~~	~~34~~	~~C~~	~~117. K.N. Shanti, B.M. Martin, S. Nagpal, D.D. Metcalfe, P.V. Subba Rao. 1993. Identification of tropomyosin as the major shrimp allergen and characterization of its IgE-binding epitopes. J. Immunol. 151:5354-5363.~~
~~Todarodes~~	~~Tod p 1; tropomyosin~~	~~38~~	~~P~~	~~117A. M. Miyazawa, H. Fukamachi, Y.~~

pacificus (squid)				Inagaki, G. Reese, C.B. Daul, S.B. Lehrer, S. Inouye, M. Sakaguchi. 1996. Identification of the first major allergen of a squid (Todarodes pacificus). J. Allergy Clin. Immunol. 98:948-953.
Haliotis Midae (abalone)	Hal m 1	49	-	117B. A. Lopata et al. 1997. Characteristics of hypersensitivity reactions and identification of a uniques 49 kDa IgE binding protein (Hal-m-1) in Abalone (Haliotis midae). J.Allergy Clin. Immunol. Submitted.
Apium graveolens (celery)	Api g 1; Bet v 1 homologue	16*	C	Z48967
	Api g 4; profilin			AF129423
	Api g 5;	55/58	P	P81943
Brassica juncea (oriental mustard)	Bra j 1; 2S albumin	14	C	118. Monsalve, R.I., M.A. Gonzalez de la Pena, L. Menendez-Arias, C. Lopez-Otin, M. Villalba, and R. Rodriguez. 1993. Characterization of a new mustard allergen, Bra j IE. Detection of an allergenic epitope. Biochem. J. 293:625-632.
Brassica rapa (turnip)	Bra r 2; prohevein-like protein	25	?	P81729
Hordeum vulgare (barley)	Hor v 1; BMAI-1	15	C	119. Mena, M., R. Sanchez-Monge, L. Gomez, G. Salcedo, and P. Carbonero. 1992. A major barley allergen associated with baker's asthma disease is a glycosylated monomeric inhibitor of insect alpha-amylase: cDNA cloning and chromosomal location of the gene. Plant Molec. Biol. 20:451-458.
Zea mays (maize, corn)	Zea m 14; lipid transfer prot.	9	P	P19656
Corylus avellana (hazelnut)	Cor a 1.0401; Bet v 1 homologue	17	C	AF136945
Malus domestica (apple)	Mal d 1; Bet v 1 homologue		C	X83672
	Mal d 3; lipid transfer protein	9	C	Pastorello
Pyrus communis (pear)	Pyr c 1; Bet v 1 homologue	18	C	AF05730
	Pyr c 4; profilin	14	C	AF129424
	Pyr c 5; isoflavone reductase			
	homologue	33.5	C	AF071477
Oryza sativa (rice)	Ory s 1;		C	U31771
Persea americana (avocado)	Pers a 1; endochitinase	32	C	Z78202
Prunus armeniaca (apricot)	Pru ar 1; Bet v 1 homologue		C	U93165
	Pru ar 3; lipid transfer	9	P	

	protein			
Prunus avium (sweet cherry)	Pru av 1; Bet v 1 homologue		C	U66076
	Pru av 2; thaumatin homologue		C	U32440
	Pru av 4; profilin	15	C	AF129425
Prunus persica (peach)	Pru p 3;lipid transfer protein	10	P	P81402
Sinapis alba (yellow mustard)	Sin a 1; 2S albumin	14	C	120. Menendez-Arias, L., I. Moneo, J. Dominguez, and R. Rodriguez. 1988. Primary structure of the major allergen of yellow mustard (Sinapis alba L.) seed, Sin a I. Eur. J. Biochem. 177:159-166.
Glycine max (soybean)	Gly m 1.0101; HPS	7.5	P	121. Gonzalez R, Varela J, Carreira J, Polo F. Soybean hydrophobic protein and soybean hull allergy. Lancet 346:48-49, 1995.
	Gly m 1.0102; HPS	7	P	121. Gonzalez R, Varela J, Carreira J, Polo F. Soybean hydrophobic protein and soybean hull allergy. Lancet 346:48-49, 1995.
	Gly m 2	8	P	A57106
	Gly m 3; profilin	14	C	AJ223982
Arachis hypogaea (peanut)	Ara h 1; vicilin	63.5	C	L34402
	Ara h 2; conglutin	17	C	L77197
	Ara h 3; glycinin	14	C	AF093541
	Ara h 4; glycinin	37	C	AF086821
	Ara h 5; profilin	15	C	AF059616
	Ara h 6; conglutin homolog	15	C	AF092846
	Ara h 7; conglutin homolog	15	C	AF091737
Actinidia chinensis (kiwi)	Act c 1; cysteine protease	30	P	P00785
Solanum tuberosum (potato)	Sol t 1; patatin	43	P	P15476
Bertholletia excelsa (Brazil nut)	Ber e 1; 2S albumin	9	C	P04403, M17146
Juglans regia (English walnut)	Jug r 1; 2S albumin	44	C	U66866
	Jug r 2; vicilin		C	AF066055
Ricinus communis (Castor bean)	Ric c 1; 2S albumin		C	P01089
OTHERS				
Anisakis simplex (nematode)	Ani s 1	24	P	A59069
	Ani s 2; paramyosin	97	C	AF173004
Ascaris suum (worm)	Asc s 1;	10	P	122. Christie, J. F., B. Dunbar, I. Davidson, and M. W. Kennedy. 1990. N-terminal amino acid sequence identity between a major allergen of Ascaris lumbricoides and

				~~Ascaris suum and MHC-restricted IgE responses to it. Immunology 69:596-602.~~
~~Aedes aegyptii (mosquito)~~	~~Aed a 1; apyrase~~	~~68~~	~~C~~	~~L12389~~
	~~Aed a 2;~~	~~37~~	~~C~~	~~M33157~~
~~Hevea brasiliensis (rubber)~~	~~Hev b 1; elongation factor~~	~~58~~	~~P~~	~~123. Czuppon AB, Chen Z, Rennert S, Engelke T, Meyer HE, Heber M, Baur X. The rubber elongation factor of rubber trees (Hevea brasiliensis) is the major allergen in latex. J Allergy Clin Immunol 92:690-697, 1993.~~ ~~124. Attanayaka DPSTG, Kekwick RGO, Franklin FCH. 1991. Molecular cloning and nucleotide sequencing of the rubber elongation factor gene from hevea brasiliensis. Plant Mol Biol 16:1079-1081.~~
	~~Hev b 2; (1,3-glucanase~~	~~58~~	~~P~~	~~123. Czuppon AB, Chen Z, Rennert S, Engelke T, Meyer HE, Heber M, Baur X. The rubber elongation factor of rubber trees (Hevea brasiliensis) is the major allergen in latex. J Allergy Clin Immunol 92:690-697, 1993.~~ ~~124. Attanayaka DPSTG, Kekwick RGO, Franklin FCH. 1991. Molecular cloning and nucleotide sequencing of the rubber elongation factor gene from hevea brasiliensis. Plant Mol Biol 16:1079-1081.~~
	~~Hev b 2; (1,3-glucanase~~	~~34/36~~	~~C~~	~~125. Chye ML, Cheung KY. 1995. (1,3-glucanase is highly expressed in Laticifers of Hevea brasiliensis. Plant Mol Biol 26:397-402.~~
	~~Hev b 3~~	~~24~~	~~P~~	~~126. Alenius H, Palosuo T, Kelly K, Kurup V, Reunala T, Makinen-Kiljunen S, Turjanmaa K Fink J. 1993. IgE reactivity to 14-kD and 27-kD natural rubber proteins in Latex-allergic children with Spina bifida and other congenital anomalies. Int Arch Allergy Immunol 102:61-66.~~ ~~127. Yeang HY, Cheong KF, Sunderasan E, Hamzah S, Chew NP, Hamid S, Hamilton RG, Cardosa MJ. 1996. The 14.6 kD (REF, Hev b 1) and 24 kD (Hev b 3) rubber particle proteins are recognized by IgE from Spina Bifida patients with Latex allergy. J Allerg Clin Immunol in press.~~
	~~Hev b 4; component of microhelix protein complex~~	~~100/110/115~~	~~P~~	~~128. Sunderasan E, Hamzah S, Hamid S, Ward MA, Yeang HY, Cardosa MJ. 1995. Latex B-serum (-1,3-glucanase (Hev b 2) and a component of the microhelix (Hev b 4) are major Latex allergens. J nat Rubb Res 10:82-99.~~

	~~Hev b 5~~	~~16~~	~~C~~	~~U42640~~
	~~Hev b 6.01 hevein precursor~~	~~20~~	~~C~~	~~M36986/p02877~~
	~~Hev b 6.02 hevein~~	~~5~~	~~C~~	~~M36986/p02877~~
	~~Hev b 6.03 C terminal fragment~~	~~14~~	~~C~~	~~M36986/p02877~~ ~~U80598~~
	~~Hev b 7; patatin homologue~~	~~46~~	~~C~~	~~Y15042~~
	~~Hev b 8; profilin~~	~~14~~	~~C~~	~~AJ132580/AJ132581~~
	~~Hev b 9; enolase~~	~~51~~	~~C~~	
	~~Hev b 10; Mn superoxide dismut~~	~~26~~	~~C~~	~~AJ249148~~
~~Ctenocephalides felis felis (cat flea)~~	~~Cte f 1;~~	~~-~~	~~-~~	~~-~~
	~~Cte f 2; M1b~~	~~27~~	~~C~~	~~AF231352~~
~~Homo sapiens (human autoallergens)~~	~~Hom s 1;~~	~~73*~~	~~C~~	~~Y14314~~
	~~Hom s 2;~~	~~10.3*~~	~~C~~	~~X80909~~
	~~Hom s 3;~~	~~20.1*~~	~~C~~	~~X89985~~
	~~Hom s 4;~~	~~36*~~	~~C~~	~~Y17711~~
	~~Hom s 5;~~	~~42.6*~~	~~C~~	~~P02538~~

[[.]]

35. (Original) The composition of claim 34, wherein the wild-type allergen is found in nature in foods, venoms, or latex.

36. (Original) The composition of claim 34, wherein the wild-type allergen is found in nature in a food selected from the group consisting of peanuts, milk, eggs, seafood, nuts, dairy products, and fruit.

37. (Withdrawn) The composition of claim 34, wherein the wild-type allergen is found in nature in bee venom.

38. (Previously presented) The composition of claim 34, wherein the wild-type allergen is an Ara h 1, Ara h 2, or Ara h 3 protein with an amino acid sequence that is encoded by the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3.

39. (Previously presented) The composition of claim 34, wherein the sequence of the modified allergen differs from the sequence of the wild-type allergen by one or more amino acid deletions, substitutions or additions within an IgE binding site of the wild-type allergen.

40. (Previously presented) The composition of claim 39, wherein the sequence of the modified allergen lacks an IgE binding site of the wild-type allergen sequence.

41. (Original) The composition of claim 34, wherein the modified allergen is located in the cytoplasm of the dead *E. coli*.

42. (Original) The composition of claim 34, wherein the modified allergen is located in the periplasm of the dead *E. coli*.

43. (Original) The composition of claim 34, wherein the modified allergen cannot be detected by antibody binding without disrupting the dead *E. coli*.

44. (Original) The composition of claim 34, wherein the composition is formulated for rectal administration.

45. (Previously presented) The composition of claim 34, wherein the dead *E. coli* was heat-killed.

46. (Previously presented) The composition of claim 34, wherein the dead *E. coli* was killed by chemical treatment.

47. (Previously presented) The composition of claim 44, wherein the dead *E. coli* was killed using a chemical selected from the group consisting of iodine, bleach, ozone, and alcohol.

48. (Previously presented) The composition of claim 34, wherein the composition is formulated for mucosal administration.

49. (Previously presented) The composition of claim 34, wherein the composition is formulated for oral administration.

Remarks

Claims 34-49 are pending in the application. Claim 37 is withdrawn from consideration. Claim 34 has been amended to list allergens in accordance with the Examiner's suggestion in co-pending application U.S.S.N. 09/731,375, and support for this amendment can be found in the Appendix that was originally filed with the specification. Claim 34 has also been amended to recite a pharmaceutically acceptable carrier that is "appropriate for rectal, vaginal, nasal, oral, buccal, or mucosal delivery," and support for this amendment can be found in the specification (see, *e.g.*, paragraphs 82-93).

No new matter has been added by the present Amendment. Applicant specifically reserves the right to pursue the subject matter of the canceled or amended claims in a related application. The present Amendment is introduced for the sole purpose of furthering prosecution. Applicant respectfully requests reexamination and reconsideration of the case in light of the present Amendment and the following Remarks. Each of the rejections levied in the Office Action is addressed individually below.

Rejection under 35 U.S.C. § 103(a) for allegedly being obvious

Claims 34-36, 38-45, 48, and 49 stand rejected under 35 U.S.C. § 103(a) on the grounds that they are obvious over PCT publication WO 99/38978 ("the '978 publication") in view of Fenton *et al.* (1995, *J. Natl. Canc. Inst.*, 87:1853-61), Vrtala *et al.* (1995, *Int. Arch. Aller. Immunol.*, 107:290-94), U.S. Patent Number 5,888,799 ("the '799 patent"), U.S. Patent Number 3,097,141 ("the '141 patent"), and Leclerc *et al.* (1990, *J. Immunol.*, 144:3174-82).

Claims 46 and 47 stand rejected under 35 U.S.C. § 103(a) on the grounds that they are obvious over the '978 publication in view of Fenton *et al.*, Vrtala *et al.*, the '799 patent, the '141 patent, and Leclerc *et al.*, and further in view of PCT Publication Number WO 92/14487 ("the '487 publication"), U.S. Patent Number 6,270,723 ("the '723 patent"), Komanapalli *et al.* (1998, *Appl. Microbiol. Biotechnol.*, 49:766-69), and/or Ingram *et al.* (1980, *J. Bacteriol.*, 144:481-88).

In Applicant's previous Responses (including the two most recent Responses submitted on February 29, 2008, and October 21, 2008), Applicant explained the many reasons that the base reference (WO 99/38978; "the '978 publication") cannot teach or suggest the claimed

invention, whether alone or in combination with various cited references. Applicant reiterates and hereby incorporates by reference all of the arguments made in previous Responses.

In the present Office Action, the Examiner provides almost 20 pages of text relating to the two § 103 rejections. Most of this text comprises the identical arguments that the Examiner has levied time and time again in this case. There is virtually no text within the § 103 rejections that provides a focused, thoughtful, or substantive response to Applicant's previous arguments. Indeed, the Examiner:

1. starts the § 103 rejection by describing the *individual teachings* of each of the references (p. 2-5 and 15-17);
2. states that one of ordinary skill in the art would have been motivated to arrive at the present claims, and then addresses each reference *individually* once again (p. 5-6 and 17-18);
3. states that "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references" (p. 7-8), which is perplexing in light of (1), (2), (5), (6), and (9);
4. copies Applicant's previously submitted arguments *verbatim* (p. 6-7);
5. *restates* the *individual* teachings of each of the references (*e.g.*, the Examiner literally *restates* the text from p.2-5 on p. 8-9);
6. *repeats* the statement that one of ordinary skill in the art would have been motivated to arrive at the present claims, and then *re*-addresses each reference *individually* once again almost verbatim (*e.g.*, the Examiner literally *restates* the text from p.5-6 on p.9-10), meanwhile asserting that the Examiner is now addressing the references as a whole;
7. (finally, but inadequately) addresses Applicant's arguments from the most recent Office Action response, buried deep with the § 103 rejection (p. 10-11);
8. addresses an argument made by Applicant in a response from several years ago, which was not made in the most recent response (p. 11-12);
9. isolates particular claim elements from the rest of the claim (*i.e.*, impermissibly considering the claim *in pieces*, rather than the claim *as a whole*) and impermissibly applies an *individual reference* to an *individual claim element* (p. 12-14);

10. cites *KSR*, concluding that the presently claimed invention was "obvious to try," that there was a reasonable expectation of success, and that the presently claimed invention is therefore obvious (p. 14-15); and
11. concludes the § 103 rejection with a discussion of *another* argument made by Applicant in a response from several years ago, which was not made in the most recent response (p. 15).

Applicant respectfully submits that this is *not* a legitimate § 103 rejection. The Examiner has not established how one of ordinary skill in the art would take the *collection of references as a whole* and arrive at the present claims. Moreover, the Examiner has made only oblique references to Applicant's previous arguments, but *has not, in fact, substantively addressed* a single one.

Indeed, the Examiner's overall strategy appears to be (a) copy and paste enormous amounts of text (relevant or not) from previous Office Actions relating to the *individual* teachings of the cited references, (b) copy and paste Applicant's arguments, (c) *re*-copy and *re*-paste all of the *identical* arguments, with a blanket statement that the Examiner is now addressing all of the references as a whole, and (d) somewhere in all of that repetitious text, make a weak attempt at addressing the substance of Applicant's arguments. Applicant has expended an enormous amount of resources trying to move prosecution forward in this case. Indeed, Applicant has (a) presented numerous arguments, (b) amended the claims several times, and (c) participated in several telephone and in-person interviews, all in an attempt to reach a meeting of the minds with the Examiner. In response to Applicant's sincere efforts, the Examiner continues to issue one Office Action after another, each one virtually identical to the one before. Applicant deserves better – Applicant is *entitled to thoughtful, substantive* prosecution that represents a valid attempt by the Examiner to join Applicant's efforts to move this case toward allowance. Applicant deserves more than a 42-page cut-and-paste job. See, *e.g.*, MPEP § 701.07(f) ("Where the applicant traverses any rejection, the examiner should, if he or she repeats the rejection, take note of the applicant's argument and *answer the substance of it*," emphasis added) and MPEP § 7.37 ("The *examiner must address all arguments* which have not already been responded to in the statement of the rejection" emphasis added).

All that being said, Applicant maintains the position that the '978 publication, whether alone or in combination with any of the cited references, does not teach or suggest a (1) modified (2) allergen (3) "encapsulated inside" (4) dead (5) *E. coli*, as recited in the present claims.

As an initial matter, Applicant points out that a proper obviousness rejection involves review of a set of references "in its entirety, i.e., as a whole" to determine *what the references fairly teach* to a *person of ordinary skill in the art* in the *absence* of the teachings of the present specification (MPEP 2141.02, section VI), particularly, what a person of ordinary skill in the art would *understand*. Applicant respectfully submits that one of ordinary skill in the art reading the *entire collection of references* levied in the § 103 rejections would *not* arrive at the presently claimed invention.

Applicant reiterates all of the arguments made in the previous Response, submitted on October 21, 2008. Although Applicant still maintains the position set forth in the previous Response, Applicant understands that all of those arguments are already part of the record and will, therefore, not repeat them here. Instead, Applicant will present new points that represent a focused, substantive attempt to address the outstanding Office Action. In particular, Applicant notes that the Examiner attempted to address some of Applicant's previous arguments on p. 10-11 of the Office Action, but the Examiner's comments demonstrated to Applicant that the Examiner has misinterpreted the teachings of the '978 reference. Applicant, therefore, provides the following observations in an attempt to clarify the teachings of the '978 reference, and requests that the Examiner either issue a Notice of Allowance or else *substantively* address *each* of these *specific* observations in the next Office Action:

1. The Examiner states that the '978 publication "teaches production of recombinant modified allergen such as modified peanut allergen Ara h 1 (Table 4), modified peanut allergen Ara h 2 (Table 2) and modified peanut allergen [*sic*] (Table 6)" (p. 11 of the Office Action). The Examiner cites p. 10, lines 10-16, and Tables 4-6 as supporting this position. Applicant respectfully submits that (a) p. 10, lines 10-16 provide a generic statement that modified allergens can be made, and (b) Tables 4-6 simply list amino acid epitopes involved with binding to IgE. Nowhere does the '978 publication actually link these two separate teachings and describe production of full-length modified protein allergens. In contrast, the present specification, for the very first time, provides such a link.

2. The Examiner states that Leclerc teaches "a pharmaceutical composition comprising heat-killed recombinant *E. coli* expressing any antigen of interest wherein the antigen is encapsulated in the periplasm" (p. 10 of the Office Action). The Examiner further states that Leclerc teaches pharmaceutical compositions, whereas the present specification does not recite pharmaceutical compositions.
   a. As an initial matter, Applicant has amended claim 34 to recite a "*pharmaceutical* composition." Since claim 34 already recited "a pharmaceutically acceptable carrier," claim 34 was already drawn to a pharmaceutical composition. Nevertheless, solely in order to further prosecution, Applicant amended claim 34 to make this clear.
   b. Applicant also amended claim 34 to specify that the pharmaceutically acceptable carrier is one that is "appropriate for rectal, vaginal, nasal, oral, buccal, or mucosal delivery." Leclerc relates *only* to methods involving injection (*i.e.*, subcutaneous or intravenous injection). Thus, one of ordinary skill in the art would not find the teachings of Leclerc to be relevant to the present claims.
   c. In addition, Applicant respectfully disagrees with the Examiner's reading of Leclerc. In contrast to the Examiner's assertion, Leclerc does *not* relate to *any* antigen of interest. Instead, Leclerc is relevant only to *viral* antigens. In contrast, the present claims relate to *allergens*, *i.e.*, substances that can elicit an allergic response. Viral antigens are not allergens. Moreover, the present claims recite a specific list of allergens, *none* of which is a viral antigen.
   d. Considering that Leclerc relates only to injection, and that it does not relate to allergens in any way, one of ordinary skill in the art would not find Leclerc relevant to the present claims *as a whole*. The Examiner cannot isolate the "encapsulated within" language from the claims, isolate the encapsulation-via-periplasm concept from Leclerc, match the two up, and throw them into the pot with the rest of the § 103 mixture.
   e. The Examiner also asserts that Leclerc teaches use of dead bacteria (p. 10 of the Office Action). However, the Examiner cannot isolate this concept from the reference as a whole any more than she can isolate the encapsulation-via-periplasm concept. Only through impermissible hindsight can one pick and

choose the desired teachings out of a reference (such as the concepts of encapsulation and dead bacteria), while discarding the undesired teachings (such as injection methods and viral antigens). The teachings of Leclerc taken *as a whole* are not relevant to the present claims and do not remedy the defects of the '978 publication.

3. The Examiner maintains the position that use of urea during the protein purification process described on p. 16 of the '978 publication necessarily means that the produced proteins are "encapsulated within" bacteria. The Examiner also alleges that this process is relevant to production of *modified* protein allergens (p. 3 of the Office Action). The Examiner states, "[t]he reference modified peanut allergen is encapsulated inside the dead *E. coli* because the recombinant modified protein is expressed as inclusion bodies which located [*sic*] in the cytoplasm since it must be solubilized with urea." This is a *complete* mischaracterization of the teachings of the '978 publication.
   a. Applicant maintains the position that the Examiner has drawn an unnecessary conclusion from the use of urea. Adding urea to lysis buffer prior to protein purification is a standard method utilized in protein purification techniques. Urea is often added to the lysis buffer irrespective of whether the protein is contained within inclusion bodies or not. Urea is often included in the lysis buffer as a *standard ingredient* simply because the scientist does not wish to make the effort to determine where the produced protein is located, so urea is included *just in case* the protein is in inclusion bodies. Whether a given lysis buffer includes urea or not is completely independent of the produced protein's location within or without a cell. The fact that the lysis buffer contains urea does not necessarily indicate that the produced protein was located in inclusion bodies. It just indicates that the scientists used urea.
   b. Moreover, as Applicant argued in the previous Response, but the Examiner completely failed to address, the protein being solubilized with urea in the '978 publication is *not a modified protein allergen* as recited in the present claims. That is, the '978 publication is describing urea purification of a *different protein*.

Even if urea were used during purification of *one* protein does *not* mean that it would be required for purification of *any* other protein.

c. Indeed, later on in the very same Office Action, the Examiner goes to great lengths to describe the theoretical *differences* between wild-type and modified allergens, and denies that Applicant has enabled production of modified allergens. Applicant respectfully submits that the *Examiner cannot have it both ways*. Either wild-type allergens are similar to modified allergens, or they are not. It is unreasonable and unfair to (1) allege that they are similar, so that production of the wild-type allergen is relevant to the § 103 position of the claims, while simultaneously alleging (2) that they are so different that Applicant's claims are not enabled or described. The Examiner needs to take a position on the relevance of the wild-type proteins to the modified proteins, and maintain a consistent position throughout the entire Office Action. The Examiner cannot change her entire position halfway through the Office Action so that it's more convenient to levy a rejection.

d. As discussed above with respect to Leclerc, the Examiner cannot isolate certain teachings from a reference and consider those teachings outside of the context of the teachings of the reference as a whole. As discussed in the previous Response, and as the Examiner completely failed to address, the *entire purpose* for using urea in the '978 publication is so that the inventors can *isolate* the expressed protein *from E. coli*. The inventors are *not* preparing dead *E. coli* so that the dead *E. coli itself* can be formulated into a pharmaceutical composition, as recited in the present claims. Instead, the inventors in the '978 publication are physically separating the produced protein allergens from the *E. coli*. Thus, considering the '978 publication as a whole, it is clear that the inventors of the '978 publication had no appreciation that the produced protein allergens could be useful *except* if and *until* they were isolated from bacterial cells.

4. The Examiner continues to pick and choose her desired teachings from all of the secondary references, leaving behind any undesirable teaching of that reference.

a. For example, the Examiner cites Fenton as teaching heat-killed recombinant *E. coli* as useful in a vaccine, but completely ignores the fact that the teachings of

Fenton *as a whole* relate to compositions and methods that result in a *mutation-specific immune response* and *teach away* from immunization using cells comprising *modified* allergens (see Response submitted on February 29, 2008).

b. The Examiner cites Vrtala as teaching bacteria transformed with "any cDNA" coding for an allergen (p. 4 of the Office Action), but completely ignores the fact that the teachings of Vrtala *as a whole* relate to compositions comprising *live Salmonella*, not *dead E. coli* (see Response submitted on February 29, 2008). Nor does the Examiner address the fact that Vrtala *et al.* (1) acknowledge and discuss the problem with live vaccines and (2) offer a solution indicate that Vrtala *et al.*, in fact, *teach away* from any other kind of solution, such as the use of dead *E. coli* as recited in the present claims (see Response submitted on February 29, 2008).

c. The Examiner cites the '799 patent as teaching use of *E. coli* as an antigen or allergen carrier for treating allergy by inducing tolerance (p. 4 of the Office Action), but completely ignores the fact that the teachings of the '799 patent *as a whole* relate to *live* bacteria.

d. The Examiner cites the '141 patent as teaching "a method of modifying anaphylactogens while retaining antigenicity of *E. coli*" (p. 4-5 of the Office Action) but completely ignores the fact that such methods have *nothing to do with* protein allergens that exhibit modified IgE-binding abilities. Indeed, the teachings of the '141 patent *as a whole* relate to "pepsin digest, oxidation, heat, and ion exchange" as a method of treating bacteria (notably, not bacteria containing therein a protein allergen) to *reduce toxicity* while retaining immunogenicity. Basically, the Examiner (using hindsight reconstruction) added this reference into the mixture because she needed to find a reference that related to *heat-killing* of bacteria, and she chose this one because it describes heat-killing of bacteria, and has some distant relatedness to immunological methods. In other words, the Examiner isolated a claim element, found a reference that mentions of that claim element, isolated that teaching from the rest of the reference, and matched the reference up with the claim. No one of ordinary skill in the art would understand the '141 patent to be relevant to the present claims.

The *most significant defect* in the Examiner's logic here is that the Examiner is not considering the *claims* as a whole, nor is the Examiner considering the teachings of the cited references as a whole. Indeed, the common thread running through all of the points detailed above is that the Examiner is *impermissibly isolating* certain elements of the claims and *matching* them up with other isolated portions of the cited references. Once the Examiner has found a "match" for each of the claim elements, the Examiner simply throws them together in a big pot and concludes that the mixture provides a *prima facie* case of obviousness. This is a textbook case of using impermissible hindsight to construct an obviousness rejection. This is *expressly forbidden* by both the courts and in the MPEP. See, *e.g.*, *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (stating that "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning" and "warning against a 'temptation to read into the prior art the teachings of the invention in issue'" (citing *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 36)) and MPEP § 2142.

For all of these reasons, the '978 publication, alone or in combination with the other cited references, cannot teach or suggest *pharmaceutical compositions* of *modified* allergens *encapsulated inside* dead *E. coli*. The Examiner cannot continue to ignore these points.

No list of secondary references, however long, is meaningful unless the cited secondary references in fact address the deficiencies of the primary reference. Moreover, the Examiner must take the teachings of the secondary references *as a whole* and may not ignore those portions that inconveniently teach away from the Examiner's intended combination, or from the claimed invention.

For all of these reasons, Applicant submits that the § 103 rejections levied in the Office Action are improper and should be removed. The present claims are not obvious over the cited art and are allowable.

Obviousness-Type Double Patenting

The Examiner has levied a *provisional* obviousness-type double patenting rejection, asserting that claims 34-36 and 38-49 pending in the present application are not patentably distinct from claims 34-45 of co-pending U.S.S.N. 10/728,051. Applicant respectfully refrains from commenting on this rejection until such time as it matures into an *actual* rejection.

Rejection under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite

Claims 34-49 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner states that the recitation of various GenBank accession numbers in claim 34 is indefinite because the nucleotide or amino acid sequences may change from time to time, while still using the same accession number. While not agreeing with the Examiner, and solely in order to further prosecution, Applicant has amended claim 34 to recite allergens in the manner which the Examiner suggested that Applicant utilize in co-pending application U.S.S.N. 09/731,375. Applicant, therefore, has amended claim 34 in accordance with the Examiner's suggestion, and respectfully requests that the rejection be removed.

Rejection under 35 U.S.C. § 112 for alleged lack of enablement and written description

The Examiner has rejected claims 34-36 and 39-47 for alleged lack of enablement, and has rejected claims 34-36 and 39-49 for alleged lack of written description. Claim 38 has not been rejected for alleged lack of enablement or written description.

In particular, the Examiner states that the specification does not provide enablement or written description for a composition comprising dead *E. coli* comprising "any 'modified allergen', any modified food allergen, any modified peanut allergens other than Ara h1, Ara h2, and Ara h3, any modified milks [*sic*] allergen, any modified eggs [*sic*], any modified seafood [*sic*], any modified nuts [*sic*], any modified dairy product [*sic*], any modified fruit allergens" (p. 20 and 32 of the Office Action). Applicant respectfully disagrees.

As an initial matter, Applicant notes that the present claims are *not* drawn to *any* modified allergen, *any* modified food allergen, *any* modified peanut allergen other than Ara h 1, Ara h 2, and Ara h 3, *any* modified milk allergen, *any* modified egg allergen, *any* modified seafood allergen, *any* modified nut allergen, *any* modified dairy product allergen, or *any* modified fruit allergens. Indeed, claim 34 explicitly recites a defined list of allergens. Applicant respectfully requests that the Examiner levy a rejection that is relevant to the subject matter *actually claimed*.

The crux of the Examiner's § 112 rejection for both enablement and written description appears to rest upon the Examiner's allegation that "[t]here is [*sic*] no specific teachings regarding which amino acids within the binding site among the genus of wild type allergen sequence [*sic*] can vary and still result in reduced ability to bind to or cross-link IgE other than the modified peanut allergen Ara h1, Ara h2, and Ara h3." (p. 28 of the Office Action). Applicant emphatically disagrees with the Examiner's allegation.

Indeed, Applicant respectfully submits that, at the time when the application was filed, the sequences of many of the allergens recited in claim 34 were known, as were the identities of the IgE epitopes contained within these allergens. To give but one example, p.6-7 of the '978 publication, over which the present application is rejected under § 103, lists published journal articles describing 56 different IgE-binding epitopes from 9 different protein allergens. Thus, it is abundantly clear that identifying the existence *and* precise location of IgE-binding epitopes is well within the grasp of one of ordinary skill in the art. Moreover, in light of the teachings of the '978 publication, identifying amino acids within such IgE-binding epitopes, mutation of which results in modified IgE-binding ability, was similarly within the grasp of one of ordinary skill in the art.

Moreover, the Examiner states that "the disclosure of a single species usually does not provide an adequate basis to support generic claims" (p. 30 of the Office Action). Fortunately, however, the present specification combined with the level of knowledge and skill in the art provides an abundance of species. As mentioned above, *at least* 56 different IgE-binding epitopes from 9 different protein allergens were known in the art when the present specification was filed, and the specification itself literally exemplifies modification of 37 different IgE-binding epitopes from 3 completely unrelated protein allergens (as argued multiple times during prosecution of this case, the fact that all three of these allergens are found in peanut does not mean that they are similar to one another).

Enablement

The legal standard for enablement is set forth in *In re Wands* (858 F.2d 731 (Fed. Cir. 1988)), which relates to production of hybridomas. The case turned on the concept of undue experimentation. The Court said that a "considerable amount of experimentation is permissible, if it is merely routine." *Id.* at 737. The Court then described the laborious experimental

procedure that would have been followed by scientists attempting to produce antibodies that were not expressly described in the *Wands* specification but that fell within the generic claims of the *Wands* application:

1. "The first step [...] is to immunize an animal." (p. 737)
2. "Next the [mouse's] spleen [...] is removed and the lymphocytes [in the spleen] are separated from the other spleen cells." (p. 737)
3. "The lymphocytes are mixed with myeloma cells, and the mixture is treated to cause a few of the cells to fuse with each other, thus creating hybridomas." (p. 737)
4. "Hybridoma cells that secrete the desired antibodies then must be isolated from the enormous number of other cells in the mixture. This is done through a series of screening procedures [of which] the first step is to separate the hybridoma cells from unfused lymphocytes and myeloma cells." (p. 737)
5. "The next step [of the screening procedures] is to isolate and clone hybridomas that make antibodies that bind to the antigen of interest. Single hybridoma cells are placed in separate chambers and are allowed to grow and divide." (p. 737)
6. "After there are enough cells in the clone to produce sufficient quantities of antibody to analyze, the antibody is assayed to determine whether it binds to the antigen." (p. 737-738)
7. Antibodies that fall within the claims are selected by determination of their "numerical affinity constant, which must be measured using the [...] laborious Scotchard analysis." (p. 738)
8. There is then performed "further screening to select those [antibodies] which have an IgM isotype and have a binding affinity constant of at least 10^9 M^{-1}." (p. 738)

The *Wands* inventors used these techniques. Some fusions were unsuccessful and produced no hybridomas; others produced hybridomas that made antibodies to the antigen of interest. Certain of these antibodies were screened. Some of the screened antibodies fell within the claims; others did not.

Despite the fact that an enormous amount of experimentation was required in *Wands* to obtain antibodies which were within the scope of the claims, the Court concluded that the experimentation was not "undue" and that the generic claims of the Wands patent were adequately enabled. The Court found that "there was a high level of skill in the art [...] and all

of the methods needed to practice the invention were well-known." *Id.* at 740. The Court also found that, although the technology involved screening hybridomas to determine which, if any, secreted antibodies with the desired characteristics, "[p]ractitioners of the art [were] prepared to screen negative hybridomas in order to find one that makes the desired antibody." *Id.* at 740. The Court did not quantify the required likelihood of success, but noted that even a success rate as low as 2.8% would not necessarily require a conclusion of undue experimentation. *Id.* at 740.

In essence, once *Wands* demonstrated that high affinity antibodies *could* be obtained, those of ordinary skill in the art could turn the experimental crank with a reasonable expectation that they too would be able to isolate such antibodies. Indeed, the very work described in the specification made clear that most antibodies found would *not* meet the claim limitations.

As was the case in *Wands*, those of ordinary skill in the art can use Applicant's examples and guidance, along with the knowledge and skill available in the art, with a reasonable expectation that they will be able to obtain other modified protein allergens with merely *routine experimentation*. The Examiner is correct that the specification does not explicitly recite all possible mutations to the claimed protein allergens. The Examiner is also correct that the not every variant produced will necessarily have the claimed binding attributes. However, a skilled person, reading the specification, in light of the knowledge and skill available in the art, would understand, indeed would explicitly be *told*, that the working examples are illustrative and instructive, and that the techniques are generalizable to the *precisely*-defined sequences (*i.e.*, IgE-binding epitopes) of other protein allergens with only routine experimentation. Such work is routine, even if laborious. Certainly, it the experimentation it requires is no more *undue* than that required in *In re Wands*.

Written Description

The legal standard for written description, as set forth in *Vas-Cath v. Mahurkar*, 935 F2d 1555, 1563-64 (Fed. Cir. 1991), is that the specification must reasonably convey to one of ordinary skill in the art that the inventor had possession of the claimed invention. It is *not necessary* to reduce every species within a claimed genus to practice in order for that claim to have adequate written description support in the specification. MPEP § 2163. Indeed, "[s]atisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or

features of the elements possessed by the members of the genus in view of the species disclosed." MPEP § 2163. In other words, the relevant question is not "did Applicant *reduce to practice* a representative number of species" but "was Applicant in *possession* of a representative number of species." Any written description analysis must therefore take into account *all* species that are described in the application, including those that were not reduced to practice.

The Examiner is correct that the specification does not explicitly set forth the sequences of all possible mutations to the IgE epitopes found within all of the protein allergens listed in claim 34. However, one of ordinary skill in the art, reading the specification, would readily recognize that the modified protein allergens presented in the specification were merely exemplary and that others would work as well. One of ordinary skill in the art would certainly appreciate that the techniques described in the specification would successfully identify all such substitutions. That is, a skilled person would understand that the present inventors were in *possession* of the invention to the full scope of claim 34.

For all of these reasons, the present claims are both enabled and described. Applicant, therefore, respectfully requests that the rejections under § 112 for alleged lack of enablement and written description be removed.

Conclusion

Applicant, therefore, respectfully submits that the present case is in condition for allowance. A Notice to that effect is respectfully requested.

If, at any time, it appears that a phone discussion would be helpful, the undersigned would greatly appreciate the opportunity to discuss such issues at the Examiner's convenience. The undersigned can be contacted at (617) 248-4903.

Respectfully submitted,

/Katherine Nicole Clouse/
Katherine Nicole Clouse, PhD
Registration Number: 62,750

Choate, Hall & Stewart LLP
Two International Place
Boston, MA 02110
t (617) 248-4903
f (617) 502-5002
nclouse@choate.com
Date: February 9, 2010